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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/04, A61K 31/435 // (C07D 471/04, 231:00, 221:00) — A1

(11) International Publication Number: **WO 95/01980**

(43) International Publication Date: 19 January 1995 (19.01.95)

(21) International Application Number: PCT/IB94/00156

(22) International Filing Date: 16 June 1994 (16.06.94)

(30) Priority Data:
08/088,292 6 July 1993 (06.07.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/088,292 (CON)
Filed on 6 July 1993 (06.07.93)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DUPLANTIER, Allen, Jacob [US/US]; 450 Pumpkin Hill Road, Ledyard, CT 06339 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

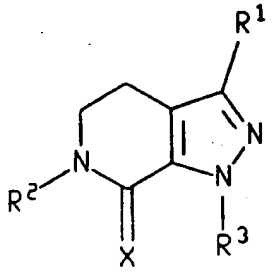
(81) Designated States: AU, BR, CA, CN, CZ, HU, JP, KR, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: BICYCLIC TETRAHYDRO PYRAZOLOPYRIDINES

(57) Abstract

Compounds of formula (I) wherein R^1, R^2, R^3 and X are as defined. The compounds of formula (I) and the pharmaceutically acceptable salts thereof are useful in inhibiting phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) and in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF.



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BICYCLIC TETRAHYDRO PYRAZOLOPYRIDINES

Background of the Invention

This invention relates to a series of bicyclic tetrahydro pyrazolopyridines which are selective inhibitors of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (hereinafter TNF) and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases; and AIDS, septic shock and other diseases involving the production of TNF.

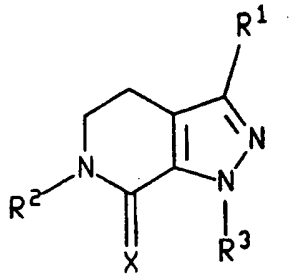
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans and to pharmaceutical compositions useful therefor.

Since the recognition that cyclic AMP is an intracellular second messenger (E.W. Sutherland, and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of the phosphodiesterases has been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J.A. Beavo and D. H. Reifsnyder, TiPS, 1990, 11, 150), and their selective inhibition has led to improved drug therapy (C.D. Nicholson, R. A. Challiss and M. Shahid, TiPS, 1991, 12, 19). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release (M.W. Verghese et al., J. Mol. Cell Cardiol., 1989, 12 (Suppl. II), S 61) and airway smooth muscle relaxation (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth muscle without causing cardiovascular effects or antiplatelet effects.

TNF is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62, S11).

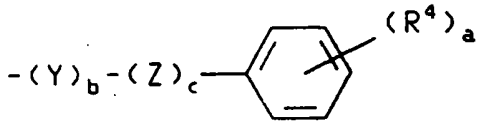
Summary of the Invention

The present invention relates to compounds of the formula



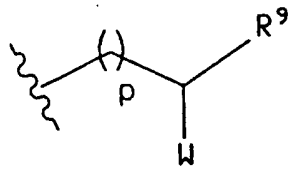
I

and the pharmaceutically acceptable salts thereof; wherein R^1 is hydrogen, (C^1-C^7)alkyl, (C^2-C^3)alkenyl, (C^3-C^5)cycloalkyl or methylene (C^3-C^5)cycloalkyl wherein each alkyl or alkenyl group may be optionally substituted with up to two (C^1-C^2)alkyl or trifluoromethyl groups or up to three halogens; X is oxygen or two hydrogen atoms; R^2 and R^3 are each independently selected from the group consisting of hydrogen, (C^1-C^{14})alkyl, (C^1-C^{14})alkoxy, (C^2-C^7)alkenyl, a (C^4-C^7)heterocyclic group containing oxygen, sulphur, SO_2 or NR^5 wherein R^5 is hydrogen or (C^1-C^4)alkyl, or a group of the formula



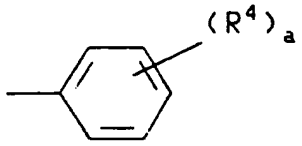
II

wherein a is an integer from 1 to 5; b and c is O or 1; R^4 is hydrogen, hydroxy, (C^1-C^5)alkyl, (C^2-C^5)alkenyl, (C^1-C^5)alkoxy, (C^3-C^6)cycloalkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C^1-C^4)alkyl; wherein Z is oxygen, sulphur, SO_2 or NR^8 wherein R^8 is hydrogen or (C^1-C^4)alkyl; and Y is (C^1-C^5)alkylene or (C^2-C^6)alkenyl optionally substituted with up to two (C^1-C^7)alkyl or (C^3-C^7)cycloalkyl groups; or a group of the formula



wherein p is an integer from 1 to 3, W is oxo or hydroxy, R^9 is (C^1-C^3)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C^1-C^2)alkyl, trifluoromethyl or halogen with the proviso that when R^1 is ethyl and R^2 is 4-methylphenyl, R^3 cannot be hydrogen, methyl, phenyl, 4-fluorophenyl or 2-pyridyl and with the proviso that when R^2 is 4-methylphenyl and R^3 is 4-fluorophenyl, R^1 cannot be phenyl, methyl or n-propyl and with the proviso that when R^1 is ethyl and R^2 is phenyl, R^3 cannot be 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl and with the proviso that when R^1 is ethyl and R^2 is 4-methoxyphenyl, R^3 cannot be 4-fluorophenyl.

In one embodiment, the invention relates to a compound of formula I wherein R^1 is (C^1-C^3)alkyl and R^2 and R^3 are each independently selected from the group consisting of (C^3-C^7)cycloalkyl, (C^4-C^7)heterocyclic group containing SO_2 or a group of the formula



III

wherein a is an integer from 1 to 5 and R^4 is hydrogen, hydroxy, (C^1-C^5)alkyl, (C^1-C^5)alkoxy or halogen.

In another embodiment, the invention relates to a compound of formula I wherein R^1 is ethyl or isopropyl; R^2 is phenyl, 2-methylphenyl, 3-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl or 3-trifluoromethylphenyl and R^3 is cyclobutyl, cyclopentyl, cyclohexyl, 3-sulfolanyl, 4-fluorophenyl or 3,4-dichlorophenyl.

The present invention further relates to a pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising a pharmaceutically effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

The present invention further relates to a method for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising administering to a patient an effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof.

The present invention further relates to a method of treating an inflammatory condition in mammals which comprises administering to said mammal an antiinflammatory amount of a compound of the formula I and the pharmaceutically acceptable salts thereof.

The present invention further relates to a pharmaceutical composition for the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising a pharmaceutically effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable carrier.

This invention further relates to a method of treating or preventing a condition selected from the group consisting of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising administering to a patient an effective amount of a compound according to formula I and the pharmaceutically acceptable salts thereof.

Specific preferred compounds of the invention are:

3-ethyl-1-(4-methoxyphenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-[3,4-c]pyridine;

3-ethyl-1-(3,4-dichlorophenyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(4-fluorophenyl)-6-(2-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclohexyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-isopropyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine.

Detailed Description of the Invention

The term "halogen", as used herein, unless otherwise indicated, includes chloro, fluoro and bromo.

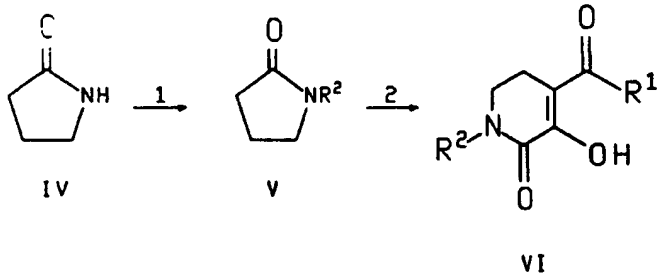
Unless indicated otherwise, the alkyl, alkoxy and alkenyl groups referred to herein may be straight chained or if comprising three or more carbons may be straight chained, branched, cyclic or a combination of cyclic and branched or straight chained moieties.

The "inflammatory diseases" which can be treated according to this invention include, but are not limited to asthma, chronic obstructive pulmonary disease, bronchitis and arthritis.

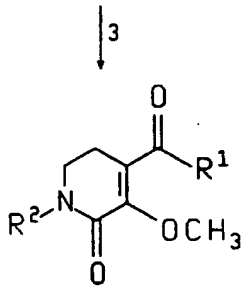
R^1, R^2 and R^3, as used herein, unless otherwise indicated, are as defined above with reference to formula I.

The following reaction schemes illustrate, but are not limiting to the preparation of the compounds of the present invention.

SCHEME 1

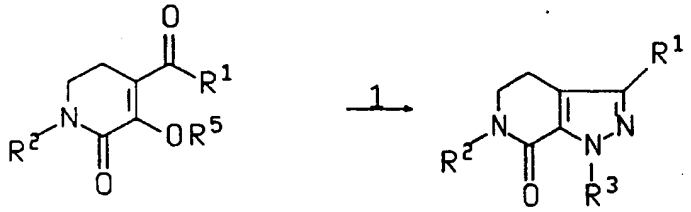


IV V VI

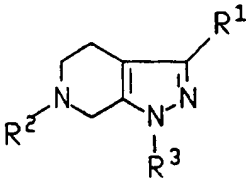


VII

SCHEME 2



VIII IX



X

In Reaction 1 of Scheme 1, the 2-pyrrolidinone compound of formula IV is converted to the corresponding N-(aryl)-2-pyrrolidone compound V wherein "aryl" is a group of the formula II by reacting IV with an aryl halide neat in the presence of copper power and potassium carbonate. Suitable aryl halides include 1-iodo- or 1-bromo- 4-methoxybenzene, 3-methoxybenzene, 2-methoxybenzene, 3-methylbenzene, 4-methylbenzene, 2-methylbenzene, 3-trifluoromethylbenzene, 2-trifluoromethylbenzene, 3,4-dimethoxybenzene or 3-cyclopentoxy-4-methoxybenzene. The reaction temperature will generally be in the range of about 110°C to about 170°C, preferably about 150°C, for a time period of about 14 hours to about 22 hours, preferably about 18 hours, under inert reaction conditions.

In Reaction 2 of Scheme 1, R^1 halide is added to a suspension of magnesium in an anhydrous aprotic solvent. The reaction mixture is heated to reflux until all the magnesium is consumed and thereafter cooled to a temperature between about -15°C to about 15°C, preferably about 0°C. The N-(aryl)-2-pyrrolidone compound of formula V is then added and the reaction mixture is warmed to room temperature while being stirred for a time period between about 1.5 hours to about 2.5 hours, preferably about 2 hours. Suitable alkyl halides include bromomethane, bromoethane or bromopropane. The preferred anhydrous aprotic solvent is anhydrous ether. Upon completion of the reaction, the desired intermediate may be isolated in a conventional manner, e.g., by first washing the combined organics with water and brine, then drying over sodium sulfate, filtering and concentrating under reduced pressure to afford a readily-recoverable precipitate in the form of a white solid.

The above precipitate is converted to the corresponding 1,2,5,6-tetrahydropyridine compound of formula VI by dispersing the precipitate in a mixture of a non-polar aprotic solvent and base. Upon vigorous stirring, ethyl oxalyl chloride is added and the reaction mixture is heated to reflux for a time period between about 1.5 hours to about 4.5 hours, preferably about 3.0 hours. The preferred non-polar aprotic solvent is benzene and the preferred base is sodium hydroxide. The solvents are removed and the resulting residue is treated with a solution of sodium alkoxide in ethanol. After heating at reflux for a time period between about 1 hour and about 3 hours, preferably about 1.5 hours, the mixture is concentrated under reduced pressure and acidified to pH=3 with hydrochloric acid.

In Reaction 3 of Scheme 1, the compound of formula **VI** is converted to the corresponding 3-methoxy-1,2,5,6-tetrahydropyridine compound **VII** by heating to reflux a reaction mixture of **VI** and 3-methyl-1-p-tolyltriazene in an aprotic solvent. The preferred aprotic solvent is 1,2-dichloroethane. The time period for the reaction is between about 30 minutes to about 120 minutes, preferably about 45 minutes.

In Reaction 1 of Scheme 2, the 1,2,5,6-tetrahydropyridine compound of formula **VIII**, wherein R^5 is hydrogen or methyl, is converted to the corresponding 4,5,6,7-tetrahydro-7-oxo-1H-pyrazolo[3,4-c]pyridine compound **IX** by reacting **VIII** with a hydrazine of the formula R^3HNNH_2. Both derivatives of the compound of formula **VIII**, 3-hydroxy and 3-methoxy, may be used as starting materials under one of three different sets of reaction conditions.

Under one set of reaction conditions, the 1,2,5,6-tetrahydropyridine compound of formula **VIII** is converted to the corresponding compound of formula **IX** by reacting **VIII** with a hydrazine hydrochloride and sodium alkoxide in an anhydrous polar protic solvent. The preferred sodium alkoxide is sodium methoxide and the preferred anhydrous polar protic solvent is anhydrous ethanol. The reaction mixture is heated to reflux for a time period between about 9 hours to about 15 hours, preferably about 12 hours.

Under a second set of reaction conditions, the 1,2,5,6-tetrahydro-pyridine compound **VIII** is converted to the corresponding compound of formula **IX** by reacting **VIII** with hydrazinobenzoic acid in an anhydrous polar protic solvent, preferably ethanol. The reaction mixture is heated to reflux for a time period between about 16 hours to about 24 hours, preferably about 20 hours. The compound **IX** so formed may be further reacted to give the corresponding 1-(4-benzamide)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine compound by reacting **IX** with sodium methoxide in a polar protic solvent, preferably methanol, for a time period between about 15 minutes to about 45 minutes, preferably 30 minutes. The polar protic solvent is removed under reduced pressure, the solid residue is suspended in a non-polar aprotic solvent, perferably benzene, and thereafter, the non-polar solvent is removed under reduced pressure. The resulting dry solid is suspended in cold ether and treated with oxalyl chloride and N,N-dimethylformamide and allowed to stir for a time period between about 30 minutes to about 90 minutes, preferably 60 minutes. The solvent is then removed and the crude residue is dissolved in dry tetrahydrofuran. The resulting

solution is added dropwise to stirred ammonium hydroxide at a temperature between about -10°C to about 10°C, preferably 0°C.

Under a third set of reaction conditions, the 1,2,5,6-tetrahydropyridine compound of formula **VIII** is converted to the corresponding compound of formula **IX** by reacting **VIII** with a hydrazine hydrochloride in a polar protic solvent, preferably methanol. The reaction mixture is heated to a temperature between about 70°C to about 110°C, preferably about 90°C, under a gentle stream of nitrogen until all of the solvent is removed. The neat mixture is then heated to a temperature between about 120°C to about 180°C, preferably about 150°C, for a time period between about 30 minutes to about 90 minutes, preferably 60 minutes.

The compounds so formed of formula **IX** may be converted to the corresponding 6-R^2-4,5,6,7-tetrahydro-7-oxo-1H-pyrazolo [3,4-c]pyridine compound, wherein R^2 is other than the group of formula **II**, by reacting a solution of **IX** in a polar aprotic solvent, preferably acetonitrile, with a solution of ammonium cerium (IV) nitrate in water at a temperature between about -15°C to about 15°C, preferably about 0°C, for a time period between about 20 minutes to about 50 minutes, preferably about 35 minutes. Upon completion of the reaction, the mixture is diluted with water and extracted with ethyl acetate. The combined organics are then washed with saturated sodium bicarbonate followed by sodium sulfite. The compound so formed in a polar aprotic solvent, preferably tetrahydrofuran, is treated with sodium hydride, heated to reflux and stirred for a time period between about 30 minutes to about 60 minutes, preferably 45 minutes. The reaction mixture is cooled to a temperature between about 20°C to about 30°C, preferably about 25°C, and an alkyl halide of formula R^2 halide, wherein R^2 is as defined with reference to formula I other than a group of formula **II**, is added. The reaction mixture is stirred and heated to reflux for a time period between about 12 hours to about 20 hours, preferably 16 hours.

In Reaction 2 of Scheme 2, the 2-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine compound **IX** is converted to the corresponding compound of formula **X** by reacting **IX** with a reducing agent, preferably lithium aluminum hydride, in a non-polar aprotic solvent, preferably ether. The reaction is stirred for a time period between about 12 hours to about 20 hours, preferably 16 hours. Water and base, preferably sodium hydroxide, is then added and the reaction mixture is stirred for a time period between

about 1.5 hours to about 2.5 hours, preferably 2 hours, and filtered. The filtrate is concentrated to a white solid.

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit phosphodiesterase IV (PDE_4) and, consequently, demonstrate their effectiveness for treating inflammatory diseases is shown by the following in vitro assay.

BIOLOGICAL ASSAY

(Human lung PDE_{IV})

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4°C. The supernatant is filtered twice through a 0.22 μm filter and applied to a Mono-Q FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_{IV} activity, determined by [^{3}H]cAMP hydrolysis and the ability of a known PDE_{IV} inhibitor (e.g. rolipram) to inhibit that hydrolysis. Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in DMSO at a concentration of 10 mM and diluted 1:25 in water (400 μM compound, 4% DMSO). Further serial dilutions are made in 4% DMSO to achieve desired concentrations. Final DMSO concentration in assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as final concentrations in assay tube).

i) 25 μl compound or DMSO (1%, for control and blank)

ii) 25 μl pH 7.5 Tris buffer

iii) [^{3}H]cAMP (1 μM)

iv) 25 μl PDE_{IV} enzyme (for blank, enzyme is preincubated in boiling water for 5 minutes)

The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water

bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES)/0.1M NaCl, pH 8.5) is added to each tube on an ice bath. The contents of each tube are applied to an Affi-Gel 601 column (Biorad Laboratories, P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [^{3}H]cAMP is washed with 2 x 6 ml washing buffer, and [^{3}H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [^{3}H].

$$\% \text{ inhibition} = 1 - \frac{\text{average cpm (test compound)} - \text{average cpm (blank)}}{\text{average cpm (control)} - \text{average cpm (blank)}}$$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of [^{3}H]cAMP to [^{3}H]5'AMP.

(TNF)

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Peripheral blood (100 mls) from human volunteers is collected in ethylenediaminetetraacetic acid (EDTA). Mononuclear cells are isolated by Ficoll/Hypaque and washed three times in incomplete HBSS. Cells are resuspended in a final concentration of 1 x 10^6 cells per ml in pre-warmed RPMI (containing 5% FCS, glutamine, pen/step and nystatin). Monocytes are plated as 1 x 10^6 cells in 1.0 ml in 24-well plates. The cells are incubated at 37°C (5% carbon dioxide) and allowed to adhere to the plates for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds (10μl) are then added to the cells at 3-4 concentrations each and incubated for 1 hour. LPS (10μl) is added to appropriate wells. Plates are incubated overnight (18 hrs) at 37°C. At the end of the incubation period TNF was analyzed by a sandwich ELISA (R&D Quantikine Kit). IC_{50} determinations are made for each compound based on linear regression analysis.

Pharmaceutically-acceptable acid addition salts of the compounds of this invention include, but are not limited to, those formed with HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3CO_2H, gluconic acid, tartaric acid, maleic acid and succinic acid. Pharmaceutically-acceptable cationic salts of the compounds of this

invention of formula I wherein R^4 is CO_2R^6 and R^6 is hydrogen include, but are not limited to, those of sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine and diethanolamine.

For administration to humans in the curative or prophylactic treatment of inflammatory diseases, oral dosages of the compounds of formula I and the pharmaceutically acceptable salts thereof (hereinafter also referred to as the active compounds of the present invention) are generally in the range of from 0.1-100 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.1 to 50 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For administration to humans for the inhibition of TNF, a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

For human use, the active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovales either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously.

For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic.

Thus in a further aspect the invention provides pharmaceutical compositions comprising a compound of the formula I and the pharmaceutically acceptable salts thereof together with a pharmaceutically acceptable diluent or carrier.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

Example 1

3-Ethyl-1-(4-methoxyphenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A mixture of 3-hydroxy-2-oxo-1-phenyl-4-propionyl-1,2,5,6-tetrahydro-pyridine (1.0 g, 4.1 mmole), 4-methoxyphenylhydrazine hydrochloride (0.8 g, 4.6 mmole) and sodium methoxide (0.11 grams, 2 mmole) in 35 ml anhydrous ethanol (distilled from Mg) was heated at reflux. After 12 hours, the solvent was removed by rotory evaporation under reduced pressure, and the crude residue was chromatographed on a 4x20 cm silica column using 1:1 ether/hexane as eluent to give 345 mg of the title compound as a red oil that crystallized upon standing at room temperature. The desired 1-(4-methoxyphenyl) regioisomer is less polar than the 2-(4-methoxyphenyl) byproduct. M.P. 43-45°C, IR (chloroform) lactam C=O, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 1.32 (t,J = 7.6 Hz, 3H), 2.74 (q, J = 7.6 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H), 3.79 (s, 3H), 4.10 (t,J = 6.6 Hz, 2H), 6.89 (d,J = 9.0 Hz, 2H), 7.22-7.39 (m, 5H), 7.45 (d,J = 9.0 Hz, 2H); Anal. calcd. for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.48; H, 6.08; N, 11.66; MS m/z (M^+) 347.

Examples 2-15

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of Example 1, affords the following compounds.

Ex.#	R^1	R^2	R^3	M.p.°C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
2	ethyl	phenyl	methyl	80-83	70.56, 6.71, 16.46	70.61, 6.77, 15.51
3	ethyl	phenyl	*tert*-butyl	120-121	72.70, 7.79, 14.13	72.50, 7.96, 14.16

4	ethyl	4-methoxy phenyl	4-methoxy phenyl	42-45	70.01, 6.14, 11.13	70.05, 6.07, 11.00
5	ethyl	4-fluoro phenyl	*tert*-butyl	92-94	(M^+) 315.1747	HRMS (M^+) 315.1741
6	ethyl	phenyl	3,4-dichloro-phenyl	(oil)	[M^+] 386.26	MS m/z [M+] 386
7	ethyl	4-fluoro phenyl	4-methoxy phenyl	129-130[a]	69.03, 5.52, 11.50	68.75, 5.37, 11.43
8	methyl	phenyl	4-fluoro phenyl	139-140[b]	[M^+] 321.3	MS m/z [M^+] 322
9	ethyl	phenyl	cyclopentyl	73-75	(M+) 309.1841	HRMS (M+) 309.1823
10	methyl	phenyl	4-methoxy phenyl	167-168	(M+) 333.1477	HRMS (M+) 333.1477
11	ethyl	phenyl	5-phenyl pentyl	(oil)	(M+) 388.2389	HRMS (M+) 388.2395
12	methyl	4-methoxy phenyl	4-fluoro phenyl	140-142[b]	68.36, 5.16, 11.96	67.92, 5.03, 11.72
13	methyl	4-methoxy phenyl	3-fluoro phenyl	133-138	68.36, 5.16, 11.96	68.04, 5.04, 11.75
14	ethyl	4-methoxy phenyl	3,4-dichloro-phenyl	50-60	60.59, 4.60, 10.09	60.34, 4.56, 9.86
15	ethyl	3-methoxy phenyl	methyl	(oil)	[M^+] 285.35	MS m/z [M^+] 286

Recrystallizing solvents: [a]isopropyl ether. [b]5% Ethyl acetate in petroleum ether.

Example 16

3-Ethyl-1-(4-phenylcarboxylic acid)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A mixture of 3-hydroxy-2-oxo-1-phenyl-4-propionyl-1,2,5,6-tetrahydro-pyridine (1.0 grams, 4.08 mmole), 4-hydrazinobenzoic acid (0.68 grams, 4.49 mmole) and 30 ml of anhydrous ethanol was heated at reflux. After 20 hours, the mixture was concentrated by rotory evaporation under reduced pressure, and the solid residue was suspended in a mixture of ethyl acetate (500 ml) and pH 4 buffer (200 ml). The organic layer was separated (leaving behind most of the 2-(4-phenylcarboxylic acid) byproduct), washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure.

Recrystallization from methanol gives 0.64 grams of the title compound as an orange solid. M.P. 261-263°C, ^{1}H NMR (300 MHz, DMSO-d^6) d 1.23 (t,J = 7.6 Hz, 3H), 2.68 (q,J - 7.6 Hz, 2H), 2.94 (t,J = 6.5 Hz, 2H), 4.05 (t,J = 6.5 Hz, 2H), 7.20-7.41 (m, 5H), 7.65 (d,J = 8.6 Hz, 2H), 7.96 (d,J = 8.6 Hz, 2H), 13.05 (s, 1H); MS m/z (M^+) 362.

Example 17

1-(4-Benzamide)-3-ethyl-6-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

To a stirred solution of sodium methoxide in methanol (prepared from 6.6 mg Na) is added 3-ethyl-6-(4-methoxyphenyl)-1-(4-phenylcarboxylic acid)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (96 mg, 0.25 mmole). After 30 minutes, methanol was removed under reduced pressure, the solid residue was suspended in benzene, and the benzene was removed under reduced pressure. The resulting dry solid was suspended in cold ether (ice-bath) and treated with oxalyl chloride (31 μl, 0.35 mmole) and anhydrous N,N-dimethylformamide (1 drop). After stirring for 1 hour the valatiles are removed under reduced pressure, and the crude residue was dissolved in dry tetrahydrofuran. The resulting solution was added dropwise to briskly stirred ammonium hydroxide at 0°C. After warming to ambient temperature over 2 hours the reaction mixture was concentrated under reduced pressure until a yellow solid begins to precipitate. At this time the mixture was diluted with water to approximately 100 ml and filtered, and the precipitate was washed with water to give 81 mg of the title compound. Decomposition point 243-245°C; ^{1}H NMR (DMSO-d_6) 1.24 (t,J = 7.6 Hz, 3H), 2.68 (q,J = 7.6 Hz, 2H), 2.93 (t,J = 6.5 Hz, 2H), 3.75 (s, 3H), 3.99 (t,J = 6.5 Hz, 2H), 6.94 (d,J = 9.1 Hz, 2H), 7.27 (d,J = 9.0 Hz, 2H), 7.43 (s, 1H), 7.59 (d,J = 8.5 Hz, 2H), 7.90 (d,J = 8.6 Hz, 2H), 8.04 (s, 1H); Anal. calcd. for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.19; H, 5.31; N, 13.55. HRMS calcd. for $C_{22}H_{22}N_4O_3$ [M^+] 391.1770. Found 391.1781.

The starting 3-ethyl-6-(4-methoxyphenyl)-1-(4-phenylcarboxylic acid)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo [3,4-c] pyridine was prepared using the appropriate reagents according to the procedure of example 16.

Example 18

1-(3,4-dichlorophenyl)-3-ethyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A stirred mixture of 3-methoxy-1-(3-methoxyphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydro-pyridine (0.49 grams, 1.7 mmole), 3,4-dichlorophenylhydrazine hydrochloride (0.40 grams, 1.87 mmole) and sodium methoxide (46 mg, 0.85 mmole) in anhydrous ethanol was heated to reflux. After 16 hours, the mixture was concentrated under reduced pressure and chromatographed on a silica gel column using 1:4 ethyl acetate/hexane as eluent to give a white solid. Recrystallization from ether gave 0.46 grams of white needles. M.P. 97-99°C, ^{1}H NMR (250 MHz, $CDCl_3$) 1.31 (t,J = 7.5 Hz, 3H), 2.73 (q,J = 7.6 Hz, 2H), 2.96 (t,J = 6.6 Hz, 2H), 3.79 (s, 3H), 4.09 (t,J = 6.6 Hz, 2H), 6.78-6.91 (m, 3H), 7.29-7.49 (m, 3H), 7.73 (d,J = 1.8 Hz, 1H); MS m/z [M+] 416.

Examples 19-42

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-methoxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of Example 18, affords the following compounds.

Ex.#	R^1	R^2	R^3	M.p.°C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found), %C, %H, %N
19	methyl	4-methoxy phenyl	3-4-dichloro-phenyl	143-144[a]	59.71, 4.26, 10.45	56.13, 4.02, 9.65
20	ethyl	3-methoxy phenyl	cyclo-pentyl	64-65	[M^+] 340.2025	HRMS [M^+] 340.2046
21	ethyl	4-methoxy phenyl	cyclo-pentyl	96-98	70.77, 7.42, 12.38	70.44, 7.68, 11.69
22	methyl	4-methoxy phenyl	cyclo-pentyl	121-122	70.13, 7.12, 12.91	69.48, 7.10, 12.70
23	iso-propyl	phenyl	3,4-dichloro phenyl	oil	[M^+] 400.0983	HRMS [M^+] 400.0966
24	ethyl	3,4-dimeth-oxyphenyl	cyclo-pentyl	107-108	[M^+] 369.46	MS m/z [M^+] 369
25	ethyl	3,4-dimeth-oxyphenyl	3,4-dichloro-phenyl	190-191[b]	59.20, 4.74, 9.41	59.41, 4.46, 9.71

Ex.#	R^1	R^2	R^3	M.p. °C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
26	iso-propyl	4-methoxy phenyl	3,4-dichloro phenyl	145-147[c]	61.40, 4.92, 9.76	61.29, 4.81, 9.53
27	propyl	4-methoxy phenyl	cyclo-pentyl	102-103[c]	71.36, 7.70, 11.89	70.98, 7.66, 11.73
28	iso-propyl	3-methoxy phenyl	3,4-dichloro-phenyl	126-127[d]	61.40, 4.92, 9.76	61.55, 5.10, 9.97
29	ethyl	4-methoxy-3-cyclo-pentoxy-phenyl	3,4-dichloro-phenyl	54-56	62.40, 5.44, 8.40	62.15, 5.50, 7.97
30	ethyl	4-methoxy-3-cyclo-pentoxy-phenyl	cyclo-pentyl	88-89	$[M^+]$ 423.55	MS m/z $[M^+]$ 423
31	ethyl	3-methoxy phenyl	4-fluoro-phenyl	139-140[e]	69.03, 5.79, 11.50	69.05, 5.42, 11.57
32	ethyl	2-methoxy phenyl	cyclo-pentyl	119-120	70.77, 7.42, 12.38	70.63, 7.16, 12.01
33	ethyl	2-methoxy phenyl	4-fluoro-phenyl	103-104[f]	$[M^+]$ 365.41	MS m/z $[M^+]$ 366
34	ethyl	3-methyl phenyl	cyclo-pentyl	oil	74.27, 7.79, 12.99	74.54, 7.89, 12.63
35	ethyl	3-methyl phenyl	4-fluoro-phenyl	oil	72.19,5.77, 12.02	72.06, 5.55, 11.52
36	ethyl	3-trifluoro-methyl-phenyl	cyclo-pentyl	oil	63.65, 5.87, 11.13	63.95, 5.73, 10.97
37	ethyl	3-trifluoro-methyl-phenyl	4-fluoro-phenyl	139-140[f]	62.53, 4.25, 10.42	62.60, 4.08, 10.41
38	ethyl	4-methyl-phenyl	cyclo-pentyl	93-94	74.27, 7.79, 12.99	74.10, 7.52, 12.59
39	ethyl	2-methyl-phenyl	4-fluoro-phenyl	141-142[b]	72.19, 5.77, 12.03	72.36, 5.52, 12.09
40	ethyl	2-methyl-phenyl	cyclo-pentyl	130-131	MW 323.44	MS m/z 323

Ex.#	R^1	R^2	R^3	M.p.°C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
41	ethyl	2-trifluoro-methyl-phenyl	4-fluoro-phenyl	48-50	MW 403.38	MS m/z 404
42	ethyl	3-methyl-phenyl	3-sulfo-lanyl	oil	MW 373.47	MS m/z 374

Recrystallizing solvents: [a] 5% Ethyl acetate/petroleum ether. [b] Isopropyl ether. [c] Ethyl acetate/hexane. [d]Ethyl ether. [e]5% Ethyl acetate/pentane. [f]Pentane.

Example 43

1-Cyclohexyl-3-ethyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 3-methoxy-1-(3-methoxyphenyl)-2-oxo-4-propionyl-1,2,5,6-pyridine (0.80 grams, 2.8 mmole) and cyclohexylhydrazine hydrochloride (0.54 grams, 3.6 mmole) in methanol (15 ml) was warmed to 90°C under a gentle stream of nitrogen until all of the solvent was removed. The neat mixture was then heated to approximately 150°C under nitrogen for 1 hour. After cooling to room temperature, the mixture was dissolved in ether and washed with 1N hydrochloric acid followed by brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on silica gel using 1:1 ethyl acetate/hexane as eluent gives 0.47 grams of the title compound as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) 1.20-1.52 (m, 6H, including t at 1.23, J = 7.6 Hz, 3H), 1.64-1.74 (m, 1H), 1.80-2.06 (m, 6H), 2.67 (q,J = 7.6 Hz, 2H), 2.87 (t,J = 6.7 Hz, 2H), 3.82 (s, 3H), 3.97 (t,J = 6.7 Hz, 2H), 5.13 (tt, J = 4.3 and 11.3 Hz, 1H), 6.79-6.93 (m, 3H), 7.31 (t,J = 8.1 Hz, 1H); HRMS calculated for $C_{21}H_{27}N_3O_2$[M^+]: 353.2103. Found: 353.2094.

Examples 44-57

Reaction of the appropriate hydrazine hydrochloride with the requisite 4-alkanoyl-3-methoxy-2-oxo-1,2,5,6-tetrahydropyridine, analogous to the procedure of Example 43, affords the following compounds.

Ex.#	R^1	R^2	R^3	M.p.°C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
44	iso-propyl	4-methoxy phenyl	cyclo-pentyl	102-103[a]	[M^+] 354	MS [M^+] 354

Ex.#	R^1	R^2	R^3	M.p. °C	Mass Spectra or Analysis (calcd.) %C, %H, %N	Mass Spectra or Analysis (found) %C, %H, %N
45	iso-propyl	3-methoxy phenyl	cyclo-pentyl	99-100[b]	71.36, 7.70, 11.89	71.10, 7.56, 11.73
46	ethyl	3-methoxy phenyl	cyclobutyl	73-74[b]	70.13, 7.12, 12.91	70.10, 7.22, 12.93
47	ethyl	phenyl	methylene cyclo-propyl	60-62[c]	73.19, 7.17, 14.23	73.34, 7.08, 13.95
48	ethyl	3-methoxy phenyl	methylene cyclo-propyl	oil	$[M^+]$ 326	MS $[M^+]$ 326
49	ethyl	4-methoxy-phenyl	phenyl	156-157[b]	72.60, 6.09, 12.10	72.35, 5.91, 12.02
50	ethyl	3-methoxy-phenyl	3-sulfo-lanyl	oil	58.59, 5.95, 10.79	58.46, 6.03, 9.82
51	ethyl	3-methoxy-phenyl	4-trifluoro-methyl-phenyl	124-125[d]	63.61, 4.85, 10.12	63.40, 4.51, 10.09
52	ethyl	3-methyl-phenyl	cyclobutyl	oil	73.75, 7.49, 13.58	73.22, 7.56, 13.03
53	ethyl	3-trifluoro-methyl-phenyl	3-sulfo-lanyl	oil	MW 427.44	MS m/z 428
54	ethyl	3-trifluoro-methyl-phenyl	cyclobutyl	oil	62.80, 5.55, 11.56	63.01, 5.54, 11.19
55	ethyl	phenyl	2-indanyl	155-156[e]	77.28, 6.49, 11.76	77.35, 6.48, 11.08
56	ethyl	2-methyl-phenyl	cyclobutyl	100-102	MW 309.41	MS m/z 310
57	ethyl	3-methoxy-phenyl	2-indanyl	60-62[f]	MW 387.48	MS m/z 388, 389, 390

Recrystallization solvents: [a]Ethyl acetate/pentane. [b]Ethyl ether/pentane. [c]Isopropyl ether/pentane. [d]Ethyl/acetate/petroleum ether. [e]Ethyl acetate. [f]Ethyl acetate/hexane.

Example 58

3-Ethyl-6-(4-fluorophenyl)-1-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

To a stirred solution of 3-Ethyl-6-(4-fluorophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.3 grams, 0.82 mmole) in 50 ml ether was added lithium aluminum hydride (33 mg, 0.86 mmole). After stirring for 16 hours water (0.5 ml) was added followed by 3N sodium hydroxide (1 ml). After stirring for 2 hours the white precipitate was filtered through celite and the filtrate is concentrated under reduced pressure. Chromatography on a silica gel column using 1:3 ethyl acetate/hexane as eluent gives 0.12 grams of the title compound as a pale yellow paste. ^{1}H NMR (250 MHz, $CDCl_3$) 1.28 (t,J = 7.6 Hz, 3H), 2.66 (q,J = 7.6 Hz, 2H), 2.71 (t,J = 5.7 Hz, 2H), 3.49 (t,J = 5.7 Hz, 2H), 3.84 (s, 3H), 4.23 (s, 2H), 6.84-6.99 (m, 6H), 7.36 (d,J = 9.0 Hz, 2H); MS m/z [M^+] 352.

Examples 59-63

Reaction of the appropriate 7-oxo-2,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine with lithium aluminum hydride, analogous to the procedure of Example 58, affords the following compounds.

Ex.#	R^1	R^2	R^3	M.p.°C	Mol. Weight	Mass Spectra [M^+] (found)
59	ethyl	4-methoxy-3-cyclopentoxy phenyl	cyclopentyl	oil	409.57	409
60	ethyl	phenyl	3,4-dichloro-phenyl	oil	372.30	371.373
61	ethyl	phenyl	cyclopentyl	oil	295.43	296
62	ethyl	3-methoxy phenyl	cyclobutyl	oil	311.43	312
63	ethyl	3-methoxy phenyl	cyclohexyl	oil	339.48	340

Example 64

1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A stirred solution of 1-cyclopentyl-3-ethyl-6-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (2.58 grams, 7.60 mmoles) in acetonitrile (90 ml) at 0°C is treated with a solution of ceric ammonium nitrate (12.5 grams, 22.8 mmoles)

in water (110 ml). After stirring for 35 minutes the mixture is diluted with water (550 ml) and extracted with ethyl acetate (100 ml x 4). The combined organics are washed with 50% saturated sodium bicarbonate (250 ml) followed by 10% sodium sulfite until the aqueous wash becomes pale yellow. The organic layer is then washed further with saturated bicarbonate and brine, and treated with decolorizing charcoal. After stirring for 30 minutes the mixture is dried over sodium sulfate, filtered through celite and concentrated under reduced pressure. The brown residue is recrystallized from ether to give .814 grams of a tan solid. M.P. 143-145°C; MS (M/Z) 234; ^{1}H NMR (250 MHz, $CDCl_3$) 1.21 (t, J = 7.6 Hz, 3H), 1.62-2.13 (m, 8H), 2.62 (q, J = 7.6 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 3.51 (dt, J = 2.7 and 6.8 Hz, 2H), 5.47 (s, 1H), 5.61 (pentet, J = 7.7 Hz, 1H).

Example 65

1-cyclopentyl-3-ethyl-6-cyclopropylmethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine

A solution of 1-cyclopentyl-3-ethyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (0.21 grams, 0.92 mmoles) in THF (5 ml) is treated with 60% sodium hydride in mineral oil (40 mg, 1.01 mmoles). After stirring at reflux over 45 minutes the reaction mixture is cooled to 25°C and (bromomethyl) cyclopropane (0.31 grams, 2.29 mmoles) is added. The mixture is stirred at reflux for 16 hours and then cooled to 25°C before concentrating under reduced pressure. Chromatography on silica gel eluting with 1:1 ethyl acetate/hexane gives 0.19 grams of the title compound as a colorless oil. MS m/z [M^+] 288; ^{1}H NMR (300 MHz, $CDCl_3$) 0.26-0.31 (m, 2H), 0.50-0.56 (m, 2H), 0.85-1.06 (m, 1H), 1.20 (t, J = 7.6 Hz, 3H), 1.62-2.08 (m, 8H), 2.61 (q, J = 7.6 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H), 3.39 (d, J = 6.9 Hz, 2H), 3.63 (t, J = 6.8 Hz, 2H), 5.67 (pentet, J = 7.8 Hz, 1H).

Preparation 1

4-Isobutyryl-3-methoxy-1-phenyl-2-oxo-1,2,5,6-tetrahydropyridine

A stirred solution of freshly distilled diisopropylamine (0.16 ml, 2.21 mmole) in anhydrous tetrahydrofuran (4 ml) was cooled to 0°C and treated with 2.5 M n-butyl lithium (0.85 ml, 2.11 mmole). After 15 minutes the mixture was cooled to -78°C and a pre-cooled solution of 4-propionyl-3-methoxy-1-phenyl-2-oxo-1,2,5,6-tetrahydropyridine (0.52 grams, 2.0 mmole) in tetrahydrofuran (4 ml) was added dropwise via cannula. After approximately 20 minutes methyl iodide (0.20 ml, 3.0

mmole) was added to the bright orange-red solution and the mixture was allowed to come to room temperature over 2.5 hours. The reaction mixture is poured into saturated aqueous ammonium chloride and the organic layer is washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography on a silica gel column using 1:4 ethyl acetate/hexane as eluent gives 0.12 grams of the title compound as a yellow oil and 0.1 grams of recovered starting material. ^{1}H NMR (250 MHz, $CDCl_3$) 1.15 (d, 6H), 2.72 (t, 2H), 3.47 (heptet, 1H), 3.82 (t, 2H), 3.97 (s, 3H), 7.21-7.45 (m, 5H); MS m/z [M^+] 274.

Preparations 2-3

Reaction of the appropriate 3-methoxy-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine with lithium diisopropylamine and methyl iodide, analogous to the procedure of preparation 1, affords the following compounds of formula **VII**.

Prep#	R^2	m.p. °C	M.W.	Mass Spectra [M^+]
2	4-methoxyphenyl	oil	303.36	304
3	3-methoxyphenyl	oil	303.36	304

Preparation 4

3-Methoxy-1-(4-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine

A solution of 3-hydroxy-1-(4-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine (5.9 grams, 23 mmole) and 3-methyl-1-p-tolyltriazine (5.1 grams, 34 mmole) in 1,2-dichloroethane was heated to reflux for 45 minutes. The mixture was allowed to cool to room temperature and was poured into water and acidified with 6N hydrochloric acid. The aqueous layer was extracted 3 times with methylene chloride, and the combined organics are washed with 1N hydrochloric acid followed by water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting quantitative brown oil was clean by thin layer chromatography and ^{1}H NMR and was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$) 1.12 (t,J = 7.2 Hz, 3H), 2.34 (s, 3H), 2.71 (t,J = 6.7 Hz, 2H), 2.93 (q,J = 7.2 Hz, 2H), 3.77 (t,J = 6.8 Hz, 2H), 3.94 (s, 3H), 7.20 (s, 4H); MS [M^+] 273.

Preparations 5-14

Reaction of the appropriate 3-hydroxy-1-aryl-2-oxo-4-alkanoyl-1,2,5,6-tetrahydropyridine with 3-methyl-1-p-tolyltriazine, analogous to the procedure of Preparation 4, affords the following compounds of formula **VI**.

Prep#	R^1	R^2	m.p. °C	M.W.	Mass Spectra [M^+]
5	ethyl	phenyl	oil	259.31	260
6	methyl	4-methoxyphenyl	oil	275.30	275
7	ethyl	4-methoxyphenyl	81-82	289.33	289
8	n-propyl	4-methoxyphenyl	oil	303.36	303
9	ethyl	3-methoxyphenyl	59-60	289.33	289, 290
10	ethyl	2-methoxyphenyl	oil	289.33	289
11	ethyl	3,4-dimethoxyphenyl	oil	319.26	319
12	ethyl	3-cyclopentoxy-4-methoxyphenyl	oil	373.45	373
13	ethyl	3-methylphenyl	oil	273.33	273
14	ethyl	3-trifluoromethylphenyl	oil	327.30	327

Preparation 15

3-Hydroxy-1-(3-methylphenyl)-2-oxo-4-propionyl-1,2,5,6-tetrahydropyridine

To a stirred suspension of magnesium turnings (1.9 grams, 79 mmole) in 30 ml of anhydrous ether was added dropwise bromoethane (5.9 ml, 79 mmole). A mild reflux was initiated after approximately 1 ml was added. After all of the magnesium was consumed, the reaction mixture was cooled to 0°C and N-(3-methylphenyl)-2-pyrrolidone (8.7 grams, 50 mmole) was added at once. After warming to room temperature and stirring for 2 hours the reaction mixture was poured over ice and extracted with ethyl acetate. The combined organics are washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 8.8 grams of a white solid.

The above solid is dispersed in a mixture of 40 ml benzene and 86 ml 1N sodium hydroxide, and with vigorous mechanical stirring ethyl oxalyl chloride (7.2 ml, 64 mmole) was added. After stirring at reflux over 1.5 hours the layers are separated and the aqueous layer was extracted with ethyl acetate. The combined organics are

washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give an amber oil. GCMS [M^+] 305.

The above intermediate was dissolved in 20 ml anhydrous ethanol and treated with a solution of sodium methoxide in methanol (prepared from the careful addition of sodium (1.0 grams) to 10 ml anhydrous methanol). After being stirred at reflux over 1.5 hours, the mixture was concentrated under reduced pressure and 100 ml of water was added. The mixture was acidified to pH 3 with 6N hydrochloric acid and the dull yellow precipitate was filtered and washed with water. Recrystallization from 75 ml isopropyl ether affords 6.8 grams of pale yellow crystals. M.P. 115-116°; ^{1}H NMR (300 MHz, $CDCl_3$) 1.16 (t,J = 7.2 Hz, 3H), 2.37 (s, 3H), 2.74-2.82 (m, 4H), 3.85 (t,J = 6.8 Hz, 2H), 7.08-7.14 (m, 3H), 7.30 (t,J = 7.7 Hz, 1H); MS m/z [M^+] 259.

Preparations 16-29

Reaction of the appropriate 2-pyrrolidinone with the requisite alkylmagnesium bromide, followed by treatment with ethyl oxalyl chloride and base, analogous to that reported in Preparation 15, affords the following compounds of formula VI.

Prep#	R^1	R^2	m.p. °C	M.W.	Mass Spectra [M^+]
16	methyl	phenyl	oil	231.25	231
17	ethyl	phenyl	140-142	245.28	245
18	ethyl	4-fluorophenyl	133-135	263.27	263
19	methyl	4-methoxyphenyl	oil	261.28	262
20	ethyl	4-methoxyphenyl	121-122	275.30	276
21	n-propyl	4-methoxyphenyl	125-126	289.33	289
22	ethyl	3-methoxyphenyl	129-130	275.30	275
23	ethyl	2-methoxyphenyl	119-120	275.30	275
24	ethyl	4-methylphenyl	110-112	259.30	260
25	ethyl	2-methylphenyl	oil	259.30	259
26	ethyl	3-trifluoromethylphenyl	117-118	313.28	313
27	ethyl	2-trifluoromethylphenyl	oil	313.28	313
28	ethyl	3,4-dimethoxyphenyl	179-180	305.33	306

Prep#	R^1	R^2	m.p. °C	M.W.	Mass Spectra [M^+]
29	ethyl	3-cyclopentoxy-4-methoxyphenyl	133-134	359.42	360

Preparation 30

N-(2-Methoxyphenyl)-2-pyrrolidone

A mixture of 2-pyrrolidone (15.0 grams, 176 mmole), 2-iodoanisole (7.6 ml, 59 mmole), copper powder (7.5 grams, 117 mmole) and potassium carbonate (8.1 grams, 59 mmole) are stirred under nitrogen at 150°C. After 18 hours, the reaction mixture was filtered through a 6x15 cm pad of silica gel eluting with 1:1 ethyl acetate/hexane to give a pale yellow oil. The unreacted reagents are removed by vacuum distillation (0.6 mm, 80-100°C) leaving 9.2 grams of the title compound as a honey-like oil. ^{1}H NMR (300 MHz, $CDCl_3$) 2.20 (pentet, 2H), 2.55 (t, 2H), 3.75 (t, 2H), 3.82 (s, 3H), 6.93-7.02 (m, 2H), 7.25-7.30 (m, 2H); MS m/z [M^+] 191.

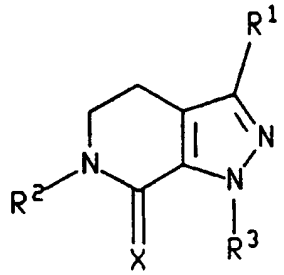
Preparations 31-39

Reactions of the appropriate iodo- or bromobenzene with 2-pyrrolidinone, analogous to that reported in Preparation 30, affords the following compounds of formula V.

Prep#	R	M.W.	Mass Spectra [M^+]
31	4-methoxyphenyl	191.22	191
32	3-methoxyphenyl	191.22	191
33	3-methylphenyl	175.23	175
34	4-methylphenyl	175.23	175
35	2-methylphenyl	175.23	175
36	3-trifluoromethylphenyl	229.20	229
37	2-trifluoromethylphenyl	229.20	229
38	3,4-dimethoxyphenyl	221.26	221
39	3-cyclopentoxy-4-methoxyphenyl	275.35	275

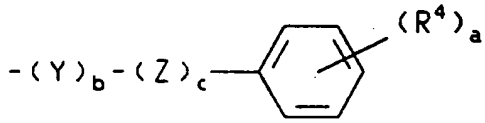
CLAIMS

1. A compound of the formula



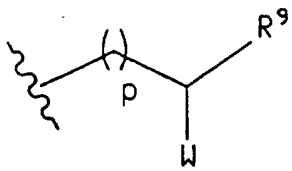
I

and pharmaceutically acceptable salts thereof; wherein R^1 is hydrogen, (C^1-C^3)alkyl, (C^2-C^3)alkenyl, (C^3-C^5)cycloalkyl or methylene (C^3-C^5)cycloalkyl wherein each alkyl or alkenyl group may be optionally substituted with up to two (C^1-C^2)alkyl or trifluoromethyl groups or up to three halogens; X is oxygen or two hydrogen atoms; R^2 and R^3 are each independently selected from the group consisting of hydrogen, (C^1-C^{14})alkyl, (C^1-C^{14})alkoxy, (C^2-C^7)alkenyl, (C^4-C^7)heterocyclic group containing oxygen, sulphur, SO_2 or NR^5 wherein R^5 is hydrogen or (C^1-C^4)alkyl, or a group of the formula



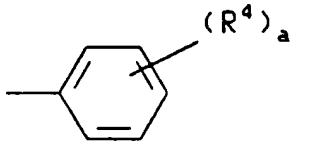
II

wherein a is an integer from 1 to 5; b and c is 0 or 1; R^4 is hydrogen, hydroxy, (C^1-C^5)alkyl, (C^2-C^5)alkenyl, (C^1-C^5)alkoxy, (C^3-C^6)cycloalkoxy, halogen, trifluoromethyl, CO_2R^6, $CONR^6R^7$, NR^6R^7, NO_2 or $SO_2NR^6R^7$ wherein R^6 and R^7 are each independently hydrogen or (C^1-C^4)alkyl; wherein Z is oxygen, sulphur, SO_2 or NR^8 wherein R^8 is hydrogen or (C^1-C^4)alkyl; and Y is (C^1-C^5)alkylene or (C^2-C^6)alkenyl optionally substituted with up to two (C^1-C^7)alkyl or (C^3-C^7)cycloalkyl groups; or a group of the formula



wherein p is an integer from 1 to 3, W is oxo or hydroxy, R^9 is (C^1-C^3)alkyl; wherein each said alkyl, alkenyl, cycloalkyl, alkoxyalkyl or heterocyclic group may be optionally substituted with one to fourteen, preferably one to five, of the group consisting of (C^1-C^2)alkyl, trifluoromethyl or halogen with the proviso that when R^1 is ethyl and R^2 is 4-methylphenyl, R^3 cannot be hydrogen, methyl, phenyl, 4-fluorophenyl or 2-pyridyl and with the proviso that when R^2 is 4-methylphenyl and R^3 is 4-fluorophenyl, R^1 cannot be phenyl, methyl or n-propyl and with the proviso that when R^1 is ethyl and R^2 is phenyl, R^3 cannot be 4-chlorophenyl, 4-fluorophenyl or 4-methylphenyl and with the proviso that when R^1 is ethyl and R^2 is 4-methoxyphenyl, R^3 cannot be 4-fluorophenyl.

2. A compound according to claim 1 wherein R^1 is (C^1-C^3)alkyl and R^2 and R^3 are each independently selected from the group consisting of (C^3-C^7)cycloalkyl, (C^4-C^7)heterocyclic group containing SO_2 or a group of the formula



III

wherein a is an integer from 1 to 5 and R^4 is hydrogen, hydroxy, (C^1-C^5)alkyl, (C^1-C^5)alkoxy or halogen.

3. A compound according to claim 1 wherein R^1 is ethyl or isopropyl; R^2 is phenyl, 2-methylphenyl, 3-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl or 3-trifluoromethylphenyl and R^3 is cyclobutyl, cyclopentyl, cyclohexyl, 3-sulfolanyl, 4-fluorophenyl or 3,4-dichlorophenyl.

4. A compound according to claim 1 selected from the group consisting of:

3-ethyl-1-(4-methoxyphenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo-[3,4-c]pyridine;

3-ethyl-1-(3,4-dichlorophenyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(4-fluorophenyl)-6-(2-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclohexyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-isopropyl-1-cyclopentyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclopentyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-(3-sulfolanyl)-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(3-trifluoromethylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine;

3-ethyl-1-cyclobutyl-6-(2-methylphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine.

5. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

6. A method for the inhibition of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF) comprising administering to a patient an effective amount of a compound according to claim 1.

7. A pharmaceutical composition for the treatment of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

8. A method of treating or preventing a condition selected from the group consisting of asthma, arthritis, bronchitis, chronic obstructive airways disease, psoriasis, allergic rhinitis, dermatitis and other inflammatory diseases, AIDS, septic shock and other diseases involving the production of TNF comprising administering to a patient an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/IB 94/00156

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 531 901 (FUJISAWA) 17 March 1993 see claims 1,9	1,5
X	FR,A,1 463 883 (CIBA) 30 December 1966 see example 3	1
X	CHEMICAL ABSTRACTS, vol. 86, no. 5, 1977, Columbus, Ohio, US; abstract no. 29733c, T. KAMETANI ET AL. 'Studies on the syntheses of heterocyclic compounds. DCLXIII. The reaction of pyridone derivatives with diazoalkane' page 362 ; see coumpoud III & CHEM. PHARM. BULL. 1976, 24(8), 1870 - 8	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1994	-5. 09. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

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		US-A-	3365459	
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